REMARKS

I. Status of the Application

Applicants note that any amendments or cancellation of claims are made without acquiescing to any of the Examiner's arguments or rejections, and solely for the purpose of expediting the patent application process in a manner consistent with the PTO's Patent Business Goals (PBG),[1] and without waiving the right to prosecute the cancelled claims (or similar claims) in the future.

Claims 1-17 were originally filed in the present application.

Applicants canceled claims 6 and 8-17, while reserving the right to prosecute these or similar claims in the future, and filed new claims 18-21 in Amendment and Response to Office Action mailed January 3, 2006.

Applicants herein amend claims 18-21, and add new Claims 22 and 23. Support for the amendments to claims 18-21 and for new Claims 22 and 23 can be found on page 20, lines 14-18 and Table 4, and in Figure 5, among other places.

Accordingly, Claims 1-5, 7 and 18-23 are pending in the application.

II. The Claims Are Definite And Supported By An Adequate Written Description

The Examiner rejected Claims 18 and 21 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite and for failing to particularly point out and distinctly claim the subject matter Applicant regards as the invention (Final Office Action, page 2). Additionally, the Examiner rejected Claim 20 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement (Final Office Action, page 2).

Applicants respectfully disagree.

Nonetheless, in order to further the prosecution of the present application, Applicants have amended Claims 18, 20, and 21. Applicants have also added new Claims 22 and 23.

In particular, amended Claim 18, and newly added independent Claim 22, recite the limitation that the reduction of the severity of inflammatory bowel disease in the subject is detectable by an improved histologic colitis score of the subject; whereas amended Claim 21

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[1] 65 Fed. Reg. 54603 (Sept., 8, 2000).

recites the limitation that the reduction of the severity of inflammatory bowel disease in the subject is detectable by a decrease in the clinical severity of colitis in the subject. Such limitations are clearly supported by the specification[2] and possess sufficient antecedent basis.[3]

Similarly, amended Claim 20, and newly added Claim 23, recite the limitation that the reduction of the severity of inflammatory bowel disease in the subject is detectable by the absence of the loss of body weight in the subject. This limitation is clearly supported by an adequate written description.[4]

Accordingly, amended Claims 18, 20 and 21, and new Claims 22 and 23, are definite and supported by an adequate written description. Applicants respectfully request that the Examiner withdraw the rejections made under 35 U.S.C. §112.

II. The Claims are Not Obvious

The Examiner rejected Claims 1-5, 7 and 18-21 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rodgers et al. (U.S. Pat. No. 6,821,953, hereinafter "Rodgers") in view of The Merck Index; and rejected Claims 1-5 and 18-21 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Acton et al. (U.S. Pat. No. 6,632,830, hereinafter "Acton") in view of The Merck Index. Applicants respectfully disagree.

In rejecting claims under 35 U.S.C. § 103, the Examiner bears the initial burden of presenting a prima facie case of obviousness.[5] A prima facie case of obviousness is established when the teachings from the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art.[6] An obviousness analysis requires that the prior art both suggest the claimed subject matter and reveal a reasonable expectation of success to one reasonably skilled in the art.[7]

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[2] See, e.g., Specification at page 20, lines 14-18 and Table 4; and Figure 5.
[3] For example, the specification defines "inflammatory bowel disease" as any of a variety of diseases characterized by inflammation of all or part of the intestines. Specific, non-limiting examples of inflammatory bowel disease provided include Crohn's disease and ulcerative colitis. See Specification at page 7, lines 26-28. Additionally, detectable symptoms of intestinal bowel disease are described (e.g., at page 8, lines 1-4) that are improved and/or prevented using a composition comprising an angiotensin converting enzyme inhibitor of the present invention.
[4] See, e.g., Specification at page 20, lines 14-18 and Table 4; and Figure 5.
[5] See In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993).
[6] In re Bell, 991 F.2d 781, 783, 26 USPQ2d 1529, 1531 (Fed. Cir. 1993).
[7] In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

Applicants respectfully submit that the cited references, individually or combined, do not suggest the claimed subject matter and do not reveal a reasonable expectation of success for carrying out the claimed invention to one reasonably skilled in the art.

A) Rodgers et al. (U.S. Pat. No. 6,821,953) and The Merck Index

The Examiner alleges that, in view of the combined teachings of Rodgers and The Merck Index, it would have been reasonable to expect a reduction in the severity of an inflammatory bowel disease following the administration of an ACE inhibitor (Final Office Action at page 4). Applicants respectfully disagree.

Specifically, the cited references do not teach, disclose or suggest the claimed subject matter nor do they provide a reasonable expectation of success for carrying out the claimed invention.

Rodgers provides a method of treating and preventing damage to mucosal tissue comprising administering to a subject an active agent comprising a peptide fragment of 3-8 amino acids. Rodgers also suggests that the method of treating and preventing damage to mucosal tissue (i.e., with an active agent comprising a peptide fragment of 3-8 amino acids) may also comprise treating with another compound for treating or preventing damage to mucosal tissue, wherein the other compound is selected from the group consisting of anti-inflammatory drugs, angiotensin converting enzyme (ACE) inhibitors, anti-infectives, growth factors, and antihistamines.

The Examiner alleges that Rodgers teaches the administration of ACE inhibitors in various inflammatory conditions of the bowel and that ulcerative colitis is one example of an inflammatory bowel disease (Final Office Action at page 3).

The Examiner does not allege that Rodgers teaches the claimed components as arranged in the claims[8], but instead simply asserts that Rodgers mentions all of the components.

This is not surprising as Rodgers does not provide any type of administration protocol for how an ACE inhibitor could be used to treat an inflammatory bowel disease (e.g., ulcerative colitis) nor does Rodgers provide any examples (*in vitro* or *in vivo*) demonstrating the use of an ACE inhibitor in the treatment of inflammatory bowel disease or short bowel syndrome. Thus,

[8] Under the law, an anticipatory reference must teach these components *as arranged in the claims*. See *In re King*, 231 USPQ 136, 138 (Fed. Cir. 1986), and MPEP 2131.

Rodgers fails to provide guidance to one of skill in the art regarding how to use an ACE inhibitor for treating an inflammatory bowel disease.

The Examiner even admits "that Rodgers fails to describe a reduction in the characteristics that define an inflammatory bowel disease, such as histological parameters, the presence of heme positive stools, weight loss and clinical severity of colitis." (Final Office Action pages 3-4).

In an attempt to overcome this deficiency, the Examiner cites to The Merck Index and its description of characteristics, such as weight loss, histological parameters, heme positive stools and clinical symptoms of inflammatory bowel disease, that can be qualitatively and quantitatively determined in a subject with inflammatory bowel disease. (Final Office Action Page 4). However, the Examiner does not allege that The Merck Index discloses or suggests the subject matter claimed in the present invention. In fact, The Merck Index does not disclose or suggest the use of an angiotensin converting enzyme inhibitor in the treatment of inflammatory bowel disease or short bowel syndrome.

From these citations alone, the Examiner alleges that, in view of the combined teachings of Rodgers and The Merck Index, it would have been reasonable to expect a reduction in the severity of an inflammatory bowel disease following the administration of an ACE inhibitor (Final Office Action at page 4). Applicants respectfully disagree.

There exists no clear direction or guidance provided by Rodgers or The Merck Index, individually or combined, rendering obvious to one of ordinary skill in the art the ability to use ACE inhibitors for the treatment of inflammatory bowel disease or short bowel syndrome, let alone a suggestion that such treatment would provide a beneficial result.

Specifically, under the Examiner's argument, it would be obvious that ACE inhibitors could be used to treat any inflammatory disease. However, this is clearly not the case. In fact, under certain circumstances, treatment with ACE inhibitors induce inflammatory disease and symptoms. For example, hundreds of cases of angioedema (an allergic, inflammatory condition of the skin characterized by patches of circumscribed swelling) related to the usage of ACE inhibitors have been reported.[9] Tongue ulcerations preceded by loss of taste have been reported

[9] See, e.g., Roberts and Wuerz RC (1991) Ann Emerg Med 20:555–558; Maier (1995) Anaesthetist 44:875–879; Vleeming et al., (1998) Drug Safety 18:171–188; Messerli and Nussberger (2000) Lancet 356:608–609.

as a complication of ACE inhibitor therapy.[10] Two cases of long-term usage of ACE inhibitors have also been associated with oral lichen planus (an inflammatory disease affecting the lining of the mouth.[11] Thus, one of ordinary skill in the art immediately appreciates that ACE inhibitors cannot be used to provide therapeutically beneficial treatment for inflammatory disease in general.

Applicants submit, for the sake of argument, that even if the references provide a generalized teaching to try to use ACE inhibitors for the treatment of inflammatory bowel disease or short bowel syndrome, that this is nothing more than an invitation to experiment and does not render obvious Applicants' invention.

In discussing obviousness in In re O'Farrell, 853 F.2d 894, 903-04, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)(citations omitted) the Federal Circuit stated:

> "The admonition that 'obvious to try' is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. . . . In others, what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it."

Applicants respectfully submit that the Examiner has not established a prima facie case of obviousness due to the inability to provide references, alone or in combination, that render obvious to one skilled in the art the use of an ACE inhibitor for the treatment of inflammatory bowel disease or short bowel syndrome. At best, the Examiner has provided evidence that it would be obvious to experiment or try administration of an ACE inhibitor in an attempt to achieve a reduction in the severity of inflammatory bowel disease in a subject.

However, "obvious to experiment" is not the standard for obviousness.[12] The Federal Circuit has made very clear that one must determine whether "the prior art would have suggested to one of ordinary skill in the art that this process **should** be carried out and **would** have a reasonable likelihood of success, viewed in light of the prior art." *Id.* at 1531 (Emphasis added).

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[10] See Nicholls et al., (1981) Ann Intern Med 94:659.
[11] See Firth and Reade (1989) Oral Surg Oral Med Oral Pathol 67:41–44.
[12] *In re Dow Chemical*, 5 USPQ2d 1529, at 1532 (Fed. Cir. 1988).

There is no reasonable expectation of success because there was no way to predict whether an ACE inhibitor could be used to achieve a reduction in the severity of inflammatory bowel disease in a subject (e.g., as evidenced by an improved histologic score or the absence of body weight loss in a subject). Applicants respectfully submit that the Examiner has improperly applied an "obvious to experiment" standard.

Thus, the Examiner has neither established that the cited references suggest the claimed subject matter nor revealed a reasonable expectation of success to one reasonably skilled in the art.

Accordingly, Applicants respectfully request that the rejection of Claims 1-5, 7 and 18-21 under 35 U.S.C. § 103(a) be withdrawn.

Similarly, the Examiner has not cited to a reference(s) that teaches, discloses or suggests a method of treating a subject comprising providing a subject with inflammatory bowel disease or short bowel syndrome, and a therapeutic composition comprising an ACE inhibitor, and administering the composition to the subject under conditions such that the severity of inflammatory bowel disease or short bowel syndrome is reduced in the subject, wherein reduction of the severity of inflammatory bowel disease in the subject is detectable by an improved histologic colitis score or the absence of body weight loss of the subject as claimed in new Claims 22 and 23. There exists no teaching within the cited references that suggests the reduction of the severity of inflammatory bowel disease in a subject, detectable by an improved histologic colitis score or the absence of body weight loss of the subject, upon administration of an ACE inhibitor. Accordingly, the cited references do not provide a reasonable expectation of success for carrying out the claimed invention. Applicants respectfully request that Claims 1-5, 7 and 18-23 be passed to allowance without delay.

B) Acton et al. (U.S. Pat. No. 6,632,830) and The Merck Index

The Examiner alleges that, in view of the combined teachings of Acton and The Merck Index, it would have been reasonable to expect a reduction in the severity of an inflammatory bowel disease following the administration of an ACE inhibitor (Final Office Action at page 5). Applicants respectfully disagree.

Specifically, the cited references do not teach, disclose or suggest the claimed subject matter nor do they provide a reasonable expectation of success for carrying out the claimed invention.

Acton provides angiotensin converting enzyme (ACE) 2 inhibitors. Specifically, Acton teaches the methods for the synthesis of various ACE-2 inhibitor compounds (See, e.g., Column 43, line 60 through Column 167, line 6).

The Examiner alleges that Acton teaches the administration of an ACE inhibitor in the treatment of an inflammatory bowel disease (Final Office Action at page 4). However, the rejection does not allege that Acton teaches the claimed components as arranged in the claims, but instead simply asserts that Acton mentions all of the components of the claimed invention. The Examiner fails to cite to language within Acton that would allow the skilled artisan background sufficient to practice the instant invention.

This is not surprising as Acton does not provide any particular examples of inflammatory bowel diseases that might benefit from administration of an ACE-2 inhibiting compound or any specific administration protocol for how an ACE-2 inhibitor could be used to treat an inflammatory bowel disease (e.g., ulcerative colitis). Acton further fails to provide any examples (*in vitro* or *in vivo*) demonstrating the use of an ACE-2 inhibitor in the treatment of inflammatory bowel disease or short bowel syndrome. Thus, Acton fails to provide guidance to one of ordinary skill in the art regarding how to use an ACE inhibitor for treating an inflammatory bowel disease.

The Examiner even admits "that Acton fails to describe a reduction in the characteristics that define an inflammatory bowel disease, such as histological parameters, the presence of heme positive stools, weight loss and clinical severity of colitis." (Final Office Action pages 4-5).

In an attempt to overcome this deficiency, the Examiner cites to The Merck Index, discussed above, and its description of characteristics, such as weight loss, histological parameters, heme positive stools and clinical symptoms of inflammatory bowel disease, that can be qualitatively and quantitatively determined in a subject with inflammatory bowel disease. (Final Office Action Page 5).

From these citations alone, the Examiner alleges that, in view of the combined teachings of Acton and The Merck Index, it would have been reasonable to expect a reduction in the

severity of an inflammatory bowel disease following the administration of an ACE inhibitor (Final Office Action at page 5). Applicants respectfully disagree.

There exists no clear direction or guidance provided by Acton or The Merck Index, individually or combined, rendering obvious to one skilled in the art the ability to use ACE inhibitors for the treatment of inflammatory bowel disease or short bowel syndrome, nor a suggestion that such treatment would provide a beneficial result.

Applicants submit, for the sake of argument, that even if the references provide a generalized teaching to try to use ACE inhibitors for the treatment of inflammatory bowel disease or short bowel syndrome, that this is nothing more than an invitation to experiment and does not render obvious Applicants' invention.

However, at best, the Examiner has provided evidence that it would be obvious to experiment or try administration of an ACE inhibitor in an attempt to achieve a reduction in the severity of inflammatory bowel disease in a subject. However, as referenced above, "obvious to experiment" is not the standard for obviousness.[13]

There can be no reasonable expectation of success because there was no way to predict whether an ACE inhibitor could be used to achieve a reduction in the severity of inflammatory bowel disease in a subject.

Applicants respectfully submit that the Examiner has not established a prima facie case of obviousness due to the inability to provide references, alone or in combination, that render obvious to one skilled in the art the use of an ACE inhibitor for the treatment of inflammatory bowel disease or short bowel syndrome.

Thus, the Examiner has neither established that the cited references suggest the claimed subject matter nor revealed a reasonable expectation of success to one skilled in the art.

Accordingly, Applicants respectfully request that the rejection of Claims 1-5 and 18-21 under 35 U.S.C. § 103(a) be withdrawn.

Similarly, the Examiner has not cited to a reference(s) that teaches, discloses or suggests a method of treating a subject comprising providing a subject with inflammatory bowel disease or short bowel syndrome, and a therapeutic composition comprising an ACE inhibitor, and administering the composition to the subject under conditions such that the severity of

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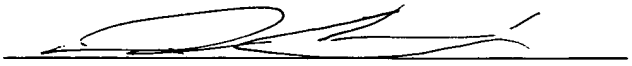
13 *In re Dow Chemical*, 5 USPQ2d 1529, at 1532 (Fed. Cir. 1988).

inflammatory bowel disease or short bowel syndrome is reduced in the subject, wherein reduction of the severity of inflammatory bowel disease in the subject is detectable by an improved histologic colitis score or the absence of body weight loss of the subject as claimed in new Claims 22 and 23. There exists no teaching within the cited references that suggests the reduction of the severity of inflammatory bowel disease in a subject, detectable by an improved histologic colitis score or the absence of body weight loss of the subject, upon administration of an ACE inhibitor. Accordingly, the cited references do not provide a reasonable expectation of success for carrying out the claimed invention. Applicants respectfully request that Claims 1-5, 7 and 18-23 be passed to allowance without delay.

CONCLUSION

For the reasons set forth above, it is respectfully submitted that Applicants have addressed all grounds for rejection and Applicants' claims should be passed to allowance. Reconsideration of the application is respectfully requested. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned collect at (608) 218-6900.

Dated: October 23, 2006



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